

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

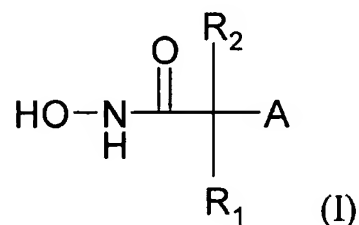
1. (Canceled)

2. (Currently Amended) A method of treating cancer in a subject in need of such treatment which comprises:

radiotherapy,

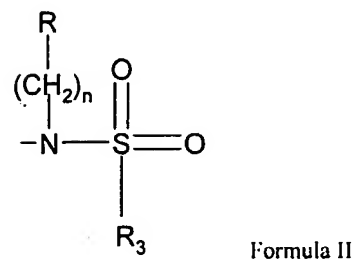
~~or cytotoxic therapy~~ a chemotherapy drug in combination with heat shock,

and further comprises administering to the subject an effective amount of a matrix metalloproteinase inhibitor of the formula I



(i) wherein

A represents substituent of formula II or III;



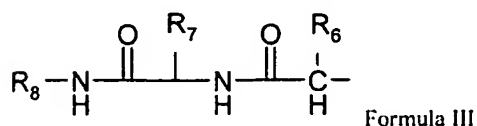
wherein

R represents hydrogen, lower alkyl, aryl-lower alkyl, aryl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, (oxa or thia)-cycloalkyl, [(oxa or thia)-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₃ represents aryl that may be unsubstituted or substituted by R₄ and R₅;

R₄ or R₅ represents independently hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, acyloxy, lower alkoxy-lower alkoxy, trifluoromethyl or cyano, oxy-C2-C3-alkylene, 1- or 2-naphthyl; or R₄ and R₅ together on adjacent carbon atoms represent lower alkylendioxy;

n represents an integer from 1 to 5;



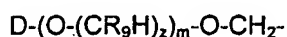
wherein

R₆ is C₃₋₁₂ alkyl, C₃₋₁₂ alkenyl, C₃₋₇(optionally hydroxy-, C₁₋₆ alkoxy-, amino-, or C₁₋₆ alkylamino-substituted) cycloalkyl, C₅₋₁₄ aryl, or C₅₋₁₄ aryl(C₁₋₆ alkyl), wherein aryl groups are optionally substituted by hydroxy-, C₁₋₆ alkyl-, C₁₋₆ alkoxy-, amino-, halo- or cyano-;

R₇ is C₁₋₁₀ (optionally hydroxy- or C₁₋₆alkoxy- amino-, C₁₋₆ alkylamino-, thiol-, C₁₋₆ alkylmercapto- or protected hydroxy-, amino- or thiol- substituted) alkyl, C₆₋₁₄ (optionally hydroxy-, C₆₋₁₄aryloxy-, or C₁₋₆alkoxy-, amino-, C₁₋₆ alkylamino-, halo-, or cyano- substituted)aryl, or indolylmethyl;

R₈ is methyl, pyridyl, or a substituent of formula X-Y- wherein X is morpholino, pyridyl or aryl, and Y is C₁₋₁₂alkylene in which up to four of the methylene (-CH₂-) units are optionally replaced with -CO-, -NH-, -SO₂- or -O-;

R₁ is hydrogen, lower alkyl, aryl, aryl-lower alkyl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, cycloalkyl-cycloalkyl, aryl-lower alkyl-lower cycloalkyl, lower alkyl-cycloalkyl, lower alkoxy-lower alkyl-cycloalkyl, aryl-cycloalkyl, cycloalkyl-lower alkyl-cycloalkyl, halo-lower alkyl-cycloalkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl, N-lower alkylpiperidyl or a substituent of formula IV



Formula IV

wherein

z is 1, 2, 3 or 4;

m is 0, 1, 2 or 3;

each R₉ is

independently H, C₁₋₁₀ (optionally hydroxy-, C₁₋₆ alkoxy-, amino-, C₁₋₆ alkylamino-, thiol-, C₁₋₆ alkylmercapto- or protected hydroxy, amino or thiol substituted) alkyl, C₂₋₆ alkenyl, C₆₋₁₄(optionally hydroxy-, C₁₋₆ alkoxy-, amino-, C₁₋₆ alkylamino-, halo- or cyano- substituted) aryl, or C₆₋₁₄ (aryl) C₁₋₆alkyl;

D is hydrogen, C₁₋₁₀ alkyl, C₆₋₁₄ aryl, C₆₋₁₄ aryl(C₁₋₆ alkyl), (C₆₋₁₄ aryl)carbonyl, or (C₁₋₁₀ alkyl)carbonyl;

R₂ is hydrogen or lower alkyl,

(ii) or wherein

R (of formula II under (a)) and R₁ together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and

R₃ and R₂ have meaning as defined under (i);

(iii) or wherein

R₁ and R₂ together with the carbon atom to which they are attached form a ring system selected from lowercycloalkane which is unsubstituted or substituted by lower alkyl, oxa-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and

R₃ and R meaning as defined under (i);

~~or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.~~

3. (Canceled)

4. (Canceled)

5. (Currently Amended) A package comprising a matrix metalloproteinase inhibitor of formula I of claim 2 (or pharmaceutically acceptable salt ~~or prodrug ester~~ thereof) together with instructions for use in combination with

~~a) radiotherapy, or~~

~~b) heat shock and cytotoxic therapy~~ a chemotherapy drug in the treatment of tumor.

6. (canceled)

7. (Canceled)

8. (Currently Amended) A method according to claim 4-2, in which the matrix metalloproteinase inhibitor is N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl) amino] -3-

methyl -butaneamide hydrochloride) monohydrate, ~~or a pharmaceutically acceptable prodrug derivative thereof~~, or a pharmaceutically acceptable salt thereof.

9. (Currently Amended) A method according to claim 4 2 in which the matrix metalloproteinase inhibitor, or a pharmacologically acceptable salt ~~or prodrug ester~~, is in the form of a enteral composition.

10. (Canceled)